area for S. dysenteriae type 1. It is likely that more cases will appear in the United States, particularly in areas adjacent to Mexico. The insidious onset, the antibiotic resistance and the organism's potential for epidemic spread present a formidable problem. The association with episodes of prolonged intestinal hemorrhages, bacteremia, renal and hepatic dysfunction and coagulation disturbances further serves to emphasize the differentiation of disease produced by S. dysenteriae type 1 from that of other Shigella serotypes. The severity of the disease stresses the necessity of early recognition and initiation of appropriate aggressive antimicrobial and supportive therapy.

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Clindamycin Colitis —An Emerging Problem

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ANTIBIOTIC THERAPY is a two-edged sword: efficacy on one edge, toxicity on the other. The benefits of a new agent are widely disseminated soon after its introduction; the toxicity, even if severe, often takes months and years to become known.

Clindamycin is a seven-deoxy, seven-chloro derivative of lincomycin, an antibiotic elaborated by an actinomycete, Streptomyces lincolnensis.[1] Gastrointestinal side effects of lincomycin therapy have been reported extensively; it has long been recognized that diarrhea is a regular accompaniment of lincomycin given by mouth.[1-4] These episodes have usually been self-limited once the offending agent was removed. More recently a pseudomembranous enterocolitis, at times fatal, has been described.[5-7] Most documented cases followed lincomycin by mouth, but a few followed parenteral administration.

Clindamycin is currently being used more and more widely as an agent for anaerobic and Gram-positive aerobic infections. Although the manufacturer's package insert and advertising include notice that penicillins remain the drugs of choice for many Gram-positive upper respiratory tract infections, clindamycin is clearly being advocated for control of many of these infections. However, this drug, like its parent, produces a diarrheal illness and recently has been incriminated with increasing frequency as a cause of pseudomembranous enterocolitis.[8-14] The incidence of diarrhea and pseudomembranous colitis are said to be distinctly lower with clindamycin than with lincomycin, although substantiation of this lower toxicity is lacking.

This paper describes the first reported fatal case of clindamycin colitis and reviews previous cases documented in the literature.

Report of a Case

A 49-year-old Mexican woman was first admitted to the Pacific Medical Center in November, 1973, for hemodialysis following six months of weekly peritoneal dialysis elsewhere for idiopathic renal failure. Peritoneal dialysis had been uneventful except for episodic pleural effusion

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thought to be secondary to dialysis. On one occasion it had been necessary to insert a tube into the left side of the chest for treatment of post-thoracentesis pneumothorax. There was history of abdominal complaints. One day before transfer, insertion of a new peritoneal dialysis catheter resulted in perforation of the transverse colon. On laparotomy a large amount of feco-purulent material was seen in the peritoneal cavity. A punctate hole in the transverse colon was closed and the abdominal cavity was thoroughly irrigated. Clindamycin was given intravenously, 600 mg three times a day for seven days. Kanamycin, 500 mg intramuscularly, was given for three doses. The postoperative course was uneventful. The patient was discharged on the 14th day, six days after cessation of clindamycin, with prescription of folic acid 1 mg daily and fluoxymesterone 10 mg daily.

The patient was readmitted five days later with complaint of abdominal pain, fever, and diarrhea, symptoms which had begun one day after discharge from hospital. At this time, the abdomen was soft, with increased non-obstructive bowel sounds and mild tenderness in the left lower quadrant. There were no masses or palpable organs. Digital rectal examination was unremarkable; sigmoidoscopy to 12 cm disclosed a uniformly erythematous, edematous, friable mucosa. Stool cultures were repeatedly negative for enteric pathogens; no ova or parasites were seen. Staphylococci were specifically sought but not found. Barium enema studies showed sigmoid diverticulosis without evidence of diverticulitis. The mucosal pattern was grossly abnormal throughout the colon and rectum, with pronounced edema and a "shaggy" mucosal pattern without definite ulcerations. An upper gastrointestinal roentgen series showed only edema of the duodenum. A diagnosis of probable clindamycin pancolitis was made and the patient was given prednisone, 40 mg daily, and psyllium hydrophilic mucilloid, 1 teaspoon twice daily. The gastrointestinal symptoms improved throughout the hospital course, and she was discharged, taking the above medications, after two revisions of her Scribner shunt. Prednisone was continued at this dosage thereafter except that methylprednisolone was given intravenously in the terminal stages of her illness.

She did well for several days at home and continued to have dialysis three times a week. However, recurrence of abdominal symptoms and the need for a new access to her circulatory system necessitated readmission after eight days. On physical examination no changes were noted. Laboratory data: glucose 245 mg, blood urea nitrogen 37 mg, total protein 5.4 grams, albumin 2.4 grams and total bilirubin 0.4 mg per 100 ml; alkaline phosphatase 152, lactic dehydrogenase 214 and serum glutamic oxalyic transaminase 54 international units; leukocytes 9,600 per cu mm, with 80 percent polymorphonuclear cells, 6 percent stab forms, 12 percent lymphocytes and 2 percent monocytes. The hematocrit was 24.1 percent and the hemoglobin content was 7.9 grams per 100 ml. Platelets were described as adequate. Urinalysis showed specific gravity of 1.010 and pH of 7.5; there were 3 white blood cells per high power field. Protein reaction was 2+. An x-ray film of the chest showed a small left pleural effusion with pleural thickening on the left which corresponded to the site of the previous chest tube placement.

Thrice weekly dialysis was continued with satisfactory control of uremia. An autologous saphenous vein graft was placed in the right arm. On proctoscopic examination the seventh hospital day, extensive involvement of the mucosa was seen, with elevated white irregular plaques on an erythematous background. Biopsy of one of these plaques showed mild chronic non-specific proctitis. Steroid and psyllium hydrophilic mucilloid therapy was continued. Frequent stools of small volume with considerable abdominal pain continued. Maintaining intravascular volume was difficult despite administration of large amounts of Plasmanate and salt-poor albumin. On the 16th hospital day, gastrointestinal bleeding was associated with disseminated intravascular coagulation (DIC). This was treated with blood, platelets and heparin, with only transient improvement. Selective celiac, superior and inferior mesenteric angiography disclosed no bleeding site. On procto-sigmoidoscopic examination the 19th hospital day there was no evidence of the plaques seen previously; the mucosa was denuded and had been replaced by granulation tissue.

Coagulase-negative staphylococcal septicemia (the primary source being an infected saphenous vein donor site) was treated with cephalothin, to which the organism demonstrated sensitivity by the pour plate method to a concentration of less than 15 mcg per ml. The patient received 12 grams of cephalothin the first day and four grams daily thereafter.

Life-threatening gastrointestinal bleeding (re-

quiring 12 units of blood) despite moderate improvement in coagulation studies led to laparotomy and colectomy with ileostomy. At this operation the entire abdomen was explored and no abscess or other pathologic process was found.

Grossly the resected colon was diffusely thickened; the mucosal surface was hyperemic and edematous, with adherent blood, beneath which were multiple elevated hemorrhagic lesions. Microscopically, there were focal hemorrhagic lesions involving the mucosa and submucosa, and vascular congestion. Fibrin thrombi were seen in a few arterioles. The overall picture was that of ischemic mucosal changes with variable amounts of reparative process. In some areas, clear mucin was seen overlying the mucosal surface, but no typical pseudomembrane was seen.

After colectomy, the patient improved for 24 hours but diffuse bleeding with DIC recurred. On the 28th hospital day, the abdomen was reexplored and there were no additional findings to explain the progressive deterioration. Death occurred on the 29th hospital day. There was no postmortem examination.

Comment

This case is similar to previously reported cases of clindamycin colitis.

The patient was female. In 11 of 15 previous case reports, the sex of the patient is mentioned; nine of these 11 were female. The reason for this apparent preponderence is obscure.

Our patient had received her last dose of clindamycin seven days before the development of abdominal symptoms. In many cases of lincomycin colitis and in at least two of the reported cases of clindamycin colitis, there were symptom-free intervals of varying length between cessation of antibiotic therapy and onset of symptoms.[7,8,14]

The route of administration of clindamycin was originally thought to be important in the pathogenesis of colitis, with disease following oral therapy in most early cases.[8,11] In this and other cases, disease followed intravenous administration.[9]

The course of the illness varies, from a week to several months of symptoms. The present case is unusual in that the course was inexorably downhill despite steroid therapy and subsequent colectomy.

The role of DIC in the patient's illness warrants comment. Her final admission to hospital was prompted by non-hemorrhagic gastrointestinal complaints. Coagulation studies did not suggest DIC until the last three weeks of her illness, five weeks after colitis began. Thus, while she died with DIC, it seems likely this was merely the final insult and not the precipitating event.

Severe protein loss and volume loss have been previously reported with this disease, and such losses were noted in our patient.[13] Although no quantitative data are available, protein-losing enteropathy is the most likely cause.

The severity of the mucosal insult varied throughout the course of our patient's illness. The initial lesion was that of a hemorrhagic friable, edematous mucosa. This was followed by development of creamy-white plaques on an erythematous background, which may be the hallmark lesion of this disorder.[7,15] Later, the mucosa was denuded and was replaced by granulation tissue; at colectomy, the changes were consistent with ischemic colitis.[16] These changes are described in previously reported patients but the changing appearance of the lesions has not been emphasized. The absence of a pseudomembrane at sigmoidoscopy therefore does not exclude the diagnosis. The radiographic features have recently been reported.[17]

Although oral glucocorticoid therapy has been used in many previous cases, its efficacy is unknown in the absence of controlled clinical trials. Our patient showed no response.

Although in other reported cases of clindamycin colitis the patient survived, many were critically ill. Scott et al reported seven cases associated with lincomycin; three of the patients died.[7] At least one of these deaths did not appear to be related to the underlying disease for which the patient received lincomycin, but to the sequelae of the colitis. Given the similarities of the drugs and the severity of the colitis produced by them, the risk of fatal colitis would appear significant.

In the case here reported, it is difficult to exclude other possible causes for the colitis. Hubbard has suggested alternate etiologic possibilities in both lincomycin and clindamycin colitis.[18] Uremia has been reported as a cause of both pseudomembranous colitis and ischemic colitis. We are not aware of such reports in patients receiving adequate hemodialysis.[15,16] Postoperative pseudomembranous enterocolitis has been described, particularly following intra-abdominal operations.[19] However, the onset of symptoms is usually earlier, averaging three and a half days after operation, compared with 15 days in the present case. Additionally, our patient received

three doses of kanamycin and it is at least possible that this drug, or a combination of the two drugs, was responsible for the severe colitis. Kanamycin is removed by hemodialysis, hence did not accumulate. Moreover, colitis with kanamycin has not been previously described. Clindamycin remains the most likely etiologic factor in this case.

The pathogenesis of the colitis with clindamycin is unknown. The parent drug, lincomycin, is thought by some investigators to exert its gastrointestinal toxicity by virtue of its relatively poor absorption (20 to 30 percent) and resultant high concentration in the large bowel. Here, either by altering the flora or by a direct toxic effect on the mucosal cells themselves, the drug is thought to cause diarrhea and sometimes pseudomembranous enterocolitis. The observation that lincomycin can cause this syndrome when given parenterally[14] is not entirely at variance with these mechanisms, since the bile is an important excretory route of lincomycin and its metabolites.

When clindamycin is given orally, absorption is about 90 percent, but excretory routes are similar to those of lincomycin. Thus, although direct toxic effect due to the presence of unabsorbed clindamycin in the large bowel is unlikely, metabolic degradation products excreted in the bile could cause toxic concentrations to be present in the gut.

The proposed mechanisms must be considered entirely spectulative at this time and do not explain why gastrointestinal toxicity develops in only a fraction of patients who are given these drugs.

Conclusion

Clindamycin has an attractive spectrum of activity against Gram-positive cocci, including penicillinase-producing straphylococci, and against Gram-negative anaerobes, including those usually resistant to penicillin (for example, Bacteroides fragilis). Colitis, which may be fulminant and life-threatening, has now been reported in at least 16 cases. The incidence of this complication is unknown, one estimate being 1 per 100,000 cases.[18] We suspect the incidence of mild to moderate colitis to be much higher. A controlled prospective trial, conceivably as a large-scale cooperative study, is the only way to establish the magnitude of the problem. This may be important to carry out, considering the frequency with which anaerobic infections are being found. When penicillin-resistant anaerobes are suspected or found, clindamycin or chloramphenicol is usually selected. The *relative* risk of toxicity with these drugs is unknown.

The role of clindamycin in antibacterial therapy remains unclear. It is preferable to use another drug for most Gram-positives infections, especially for minor infections and most skin and upper respiratory infections. Clindamycin should be reserved for serious infections likely to be caused by Bacteroides fragilis or other penicillin-resistant anaerobes.

Summary

A case of fatal pancolitis following seven days of parenteral clindamycin therapy for colon perforation is presented. Fifteen previously reported cases of "clindamycin-colitis" are reviewed. The sex incidence (female predominance) and occurrence following parenteral *or* oral administration are noted. The clinical course and proctosigmoidoscopic findings are widely varied. Glucocorticoid therapy is not of proven efficacy. The need for additional information regarding the incidence of this side effect of clindamycin is evident.

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